REMARKS

I. Status of Claims and Objections

Claims 12-19, 20-22, 25 and 28-32 are pending. Claims 12-19 are under examination. Claims 20-22, 25 and 28-32 are withdrawn. Claims 33-38 are new. Support for these claims is found in the original claims and, e.g. at page 7, lines 5-11 (conservatively replaced amino acids). Applicants maintain their right to rejoinder of remaining method claims 20-22, 25 and 28-32 upon allowance of the claims 12-19 from which they depend. Applicants maintain their traversal of the restriction requirement on the grounds that it would not be an undue burden to examine all of the claims together.

Claims 12-21, 25, and 28-30 have been amended to correct informalities. All amendments made herein are without prejudice to Applicants' right to pursue claims of original or similar scope in a duly filed continuing application.

II. Rejection under 35 U.S.C. §101

Claims 17-19 and 28-30 are rejected under 35 U.S.C. §101 for assertedly being directed to non-statutory subject matter. Office Action at page 2. Applicants' respectfully disagree.

Claims 12-14, from which claims 17-19 and 28-30 depend, were amended previously to recite "isolated" polynucleotides, which obviated a previous rejection under 35 U.S.C. §101. Because the polynucleotides are "isolated" in independent claims 12-14, the dependent claims directed to vectors and host cells comprising the "isolated" polynucleotides of claims 12-14 also must have been touched by the hand of the inventor. Consequently, the rejection is overcome and must be withdrawn.

III. Rejection under 35 U.S.C. §112, second paragraph

Claims 12-19 and 28-30 were rejected under 35 U.S.C. §112, second paragraph, for assertedly ambiguous language. Office Action at page 3.

In response, Applicants have amended claims 12-14 to remove asserted ambiguities in interpretation of the claims. Applicants submit that the amended claims are clear and the rejection may be withdrawn.

IV. Rejection under 35 U.S.C. §112, first paragraph

Enablement

Claims 12-16 were rejected under 35 U.S.C. §112, first paragraph, for assertedly lacking enablement for TCRs comprising CDRs having up to three replacement residues relative to the CDR sequences recited in the claims. Office Action at pages 4-7. Applicants respectfully traverse for the reasons of record and the reasons set out below.

A specification disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991).

Applicants' discovery of a TCR which binds to a Wilms tumor-specific peptide, and which mediates killing of tumor cells when transfected into other T cells, enables one of ordinary skill in the art to make other versions of the TCR that retain affinity or may even have greater affinity for this tumor-specific peptide. Applicants provide evidence herewith that, as of the effective filing date of the present application, the skilled person could routinely modify the disclosed CDR sequences and test the modified TCR for binding to an HLA-A2/RMFPNAPYL (SEQ ID NO: 1) complex. Procedures for such sequence modifications are well known in the art and have been successfully carried out for a number of different polypeptides. For example, affinity maturation of TCRs, where mutations are introduced into the CDRs using random or directed mutagenesis and, e.g. phage display or yeast display, is well known in the art. Moreover, procedures for selecting sequences which retain their TCR recognition specificity are well known in the art. Given that such variations in a limited number of amino acids in a TCR are so routine and easily carried out, it would be unfair to Applicants to limit their claims to particular CDR sequences. Applicants should have a reasonable degree of protection for the claimed subject matter.

Because the Examiner was unsatisfied with the Li reference (provided as Exhibit A in the previous response of record), Applicants herewith provide additional evidence (Holler et al. (Proc. Natl. Acad. Sci. USA, 97:5387-92, 2000; hereinafter "Holler;" Exhibit A) that

confirms that making TCRs comprising modified CDRs was known in the art at the time of the invention. Holler, several years prior to the filing date of the instant application, disclosed a strategy for engineering TCRs that can be used in targeting TCRs to specific peptide/MHC complexes for diagnostic and therapeutic purposes. More specifically, Holler describes an *in vitro* method for the directed evolution of high-affinity TCRs. Holler reported the use of directed mutagenesis to *vary five of seven amino acids in the CDR* to produce TCRs with 100-fold higher intrinsic binding affinities for ligand (see page 5387, column 2). Thus, contrary to the Examiner's assertion, methods for engineering TCRs with increased affinity for cognate peptides were routine as of Applicants filing date. Clearly it would have been a simple matter to engineer TCRs that retained the same affinity. Thus, it would not require undue experimentation to use the methods described by Holler along with the teachings in the instant specification for the skilled person (1) to carry out mutagenesis on the CDR sequences recited in the claims, (2) make up to three amino acid replacements in one or more CDRs, and (3) arrive at a TCR molecule that retains or has even greater affinity for the HLA-A2/RFMPNAPYL complex.

Another factor weighing in favor of concluding that the claims are enabled is the relative skill of those in the art, which is generally recognized as being quite high. One of skill in the art can readily use a process *of in vitro* evolution, and related techniques, to generate TCRs that retain peptide specificity. Given the base sequence information of the CDR polypeptides (SEQ ID NOS: 2, 3, 5, 6, 7, and 9), the specifically identified functional outcome from a mutation to that sequence (retained affinity for an HLA-A2/RMFPNAPYL (SEQ ID NO: 1) complex), and the well-known techniques in the art for making modified polynucleotides and polypeptides and measuring binding affinities, one skilled in the art clearly would be able to carry out the methods of the invention using no more than routine experimentation.

Finally, the specification provides guidance on how to go about making mutations. For example, the specification at page 7, lines 5-11 teaches that one can begin by varying 1, or two, or more amino acids in a CDR, and may proceed to vary amino acids in other CDRs. The specification also teaches at page 7, lines 9-11 that one may "typically" begin with conservative substitutions, which have a relative high likelihood of providing variants that retain the properties of the original polypeptide because as the replacement amino acids have

the same or similar properties. The specification notes at page 7, lines 13-29 that the structure of TCRs is well known in the art and provides reviews that can be used to design variants. The specification describes methods of carrying out mutagenesis on CDR regions (page 7, lines 13-29, and page 14, lines 11-17). Finally, the specification also teaches at page 8, lines 1-4, that the functional avidity of TCR molecules expressed in T cells can be measured by peptide titration experiments as outlined by Gao et al, *Blood* 95:2198-2203, 2000. The specification discloses not only the antigen, HLA-A2, but also the specific antigen sequence, RMFPNAPYL (SEQ ID NO: 1), which binds the TCR. Thus, the specification provides guidance to one of skill in the art to make and identify TCR molecule variants with the claim-recited properties using well known techniques without undue experimentation.

Applicants remind the Examiner that all dependent claims should be considered separately and examined with specificity. In particular, dependent claims 33, 35 and 37 limit the number of changes (e.g. 3/50 or 94% identity) that can be made to the CDRs. Similarly, dependent claims 34, 36 and 38 recite conservatively replaced amino acids, which as noted above is likely to provide variants that retain the properties of the original polypeptide.

For all the reasons set out above, the claims are enabled and the rejection should be withdrawn.

Written description

Claims 12-14, 15-19, and 28-30 were rejected under 35 U.S.C. §112, first paragraph, for assertedly lacking written description for a genus of polynucleotides encoding TCRs with modified alpha and beta chains that bind to an HLA-A2 presenting peptide RMFPNAPYL (SEQ ID NO: 1) with greater affinity than unmodified TCR. Office Action at pages 7-11. In response, Applicants respectfully disagree.

There is a strong presumption that an adequate written description of the claimed invention (i.e., claims) is present when the application is filed. *In re Wertheim,* 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976); *see* also M.P.E.P. §2163 (I)(A).

Further, M.P.E.P. § 2163 provides that:

> [a]n applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties,

> functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem,* 323 F.3d 956, 964 (Fed. Cir. 2002).

Here the disclosure meets this threshold standard. The specification describes the claimed genus of polynucleotide compounds by a combination of characteristics, including polynucleotide and encoded polypeptide structures, and functional characteristics that are sufficiently detailed and correlated to structure so that one of skill in the art will recognize the claimed genus of compounds. Moreover, Applicants have provided a description of a number of conservative substitutions, as noted above, that make up a representative number of species for the genus.

Applicants have disclosed the specific polypeptide sequences for each of the CDRs in the TCR molecules. Applicants have disclosed the specific antigen, HLA-A2, and antigen sequence, RMFPNAPYL (SEQ ID NO: 1), which binds the TCR. The specification provides the polynucleotides encoding the alpha and beta chains of the TCR (Figures 1 and 3); the polypeptides of the alpha and beta chains of the TCR and the positions of the CDRs, framework regions, and constant regions (Figures 2 and 4); methods of carrying out mutagenesis on CDR regions (page 7, lines 13-29, and page 14, lines 11-17); and methods of measuring binding of TCR to the HLA-A2 presenting peptide by peptide titration experiments as outlined by Gao et al, *Blood* 95:2198-2203, 2000 (page 8, lines 1-4).

Contrary to the Examiner's assertion at page 11 of the Office Action, Applicants have provided evidence that this is not an invention in an unpredictable art and there is not substantial variation within the genus of claimed polynucleotides (e.g., wherein only up to three amino acid residues in one or more of the encoded CDR polypeptides may be replaced).

Applicants remind the Examiner that all dependent claims should be considered separately and examined with specificity. In particular, dependent claims 33, 35 and 37 limit the number of changes (e.g. 6/50 or 94% identity) that can be made to the CDRs. Similarly, dependent claims 34, 36 and 38 recite conservatively replaced amino acids, for which a representative number of different species are described.

Thus, the instant application provides the necessary description of structure and function to show that the Applicants were in possession of the genus of polynucleotides as claimed. Therefore, the rejection for lack of written description may properly be withdrawn.

Conclusion

The Examiner is invited to contact the undersigned should further discussion expedite allowance of the claims.

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Respectfully submitted,

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